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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/670,701	SU ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7 and 9-34* is/are pending in the application.

4a) Of the above claim(s) *4 and 27-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7 and 9-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-3, 5, 7, 9-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleve et al (Mol. Cell. Probes (1998) 12:243-147) in view of Dimitrov et al (U.S. PgPub 2003/0013091).

Cleve teaches a method of claims 1 and 12 comprising:

(a) obtaining a barcode comprising two or more tags attached to an organic molecule backbone (see page 245, columns 1 and 2, where the branched DNA amplifier molecule has 15 branches with four copies of a sequence which bind to

labelled probes, where binding of the labelled probes will result in two or more tags attached in a noncovalent manner to an organic molecule backbone),

(b) binding the barcode to a target (see page 245, column 2, where the probes are hybridized to a target),

(c) detecting the barcode bound to the target (see page 246, subheading "Flow Cytometry", where the barcodes are individually detected).

Wherein the organic molecule backbone comprises one or more branched nucleic acids (see page 245, column 1 and 2, where branched nucleic acids with 15 branches are used which are organic molecules) and

The barcode is detected by a technique of fluorescence spectroscopy (see figure 1, and page 246, column 1, where fluorescence spectroscopy is used to measure the beads).

With regard to claims 2-3, Cleve teaches single stranded nucleic acid probes (see page 245, columns 1 and 2, where the probes are single stranded).

With regard to claim 5, Cleve teaches the use of a fluorescent dye such as fluorescein (see page 246, column 2, where fluorescein is, of course, a fluorescent dyes, but also will function as a Raman tag).

With regard to claim 7, Cleve teaches branched nucleic acids where the branches are a predetermined locations on the backbone (see page 245, columns 1 and 2).

With regard to claim 9, Cleve teaches that the barcode binds via the oligonucleotide probe (see page 245, column 2).

With regard to claims 11, 13, 14, 25, 26, Cleve teaches a nucleic acid target and detection of the binding to the target (see page 245, column 2).

With regard to claim 15, 21, 24, Cleve teaches that four monomeric copies of the labelled probe will be noncovalently linked to the branched DNA to form a polymeric labeled branched DNA (see page 245, columns 1 and 2)

With regard to claim 16, Cleve teaches monomeric units with fluorescein, which is a Raman tag (see page 246, column 2)

With regard to claims 22-23, Cleve teaches binding of the branched DNA to a bead by a capture probe (see page 245, column 2).

Cleve does not teach the use of a plurality of barcodes on the branched DNA nor the situation where the number of barcodes exceeds the number of different types of tags.

Dimitrov expressly teaches the use of a plurality of barcodes since Dimitrov teaches that "Several unique combinations of labels can be formed using branched nucleic acids (see page 7, paragraph 0057)." Dimitrov further notes that "nucleic acids labeled with any or all of these combinations can be bound to another nucleic acid through hybridization (see page 7, paragraph 0055)."

Dimitrov further teaches the situation where the number of barcodes exceeds the number of different types of tags. Dimitrov expressly states "In this invention, various ratios of different label monomers bound to

nucleic acids can be combined to generate a diverse population of unique labels that can include up to 10^{17} or more unique labels. For example, a nucleic acid labeled with two fluorescein labeled nucleotides and three rhodamine labeled nucleotides will emit light at a different wavelength compared to a nucleic acid labeled with three fluorescein nucleotides and two rhodamine nucleotides. In another example, a nucleic acid could be labeled with different ratios of three or more label monomer:nucleotides which greatly increases the variety of unique labels that can be generated (see paragraph 0065)." So Dimitrov expressly teaches the situation where ratios of different labels are combined to provide a much larger number of different tags. Dimitrov recognizes that up to 10^{17} or more unique labels can be formed by the use of ratios of a much small number of labels.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cleve to use the multi fluor branched DNA labels of Dimitrov since Cleve expressly motivates the use of different colors, stating "In addition, the principle of FCM quantitation can be expanded to take advantage of the technology's unique strengths: through the use of software tools, beads of different colours or different sizes can be quantitated separately (see page 244, column 1)." Thus, Cleve directly motivates the use of different colors in the analysis assay and Dimitrov addresses this ability with the branched DNA labels that can differ in color to "provide an accurate and sensitive system for the detection and quantitation of analytes in a mixture (see page 2, paragraph 10)." An ordinary

practitioner would have been motivated to use the multifluor branched DNA probes of Dimitrov in the branched DNA assay of Cleve in order to permit multiplex detection of different analytes in a mixture as taught by Dimitrov and as motivated by Cleve, who desired to detect both HIV and cytomegalovirus (see page 247, column 1, for example) in a single reaction.

4. Claims 1-3, 5, 7, 9-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singer et al (U.S. Patent 6,534,266) in view of Urdea et al (U.S. Patent 5,635,352) and further in view of Horn et al (U.S. 2001/0009760).

Singer teaches a method of claims 1 and 12 comprising:

(a) obtaining a plurality of barcodes, at least one of the plurality of barcodes comprising two or more different tags attached to an organic molecule backbone (see column 8, lines 6-38, where oligonucleotides have five different fluorophores attached to the nucleic acid probe backbone to form 31 different barcodes),

(b) binding at least one of the plurality of barcodes to a target (see column 8, lines 39-43, where the probes are hybridized to a target),

(c) detecting at least one of the plurality of barcodes bound to the target (see column 8, lines 44-57, where the barcodes are individually detected).

Wherein the barcodes are detected by fluorescence spectroscopy (see column 9, lines 5-20) and wherein the number of barcodes in the plurality of barcodes exceed the number of different types of tags attached to the plurality of barcodes (see column 8, lines 16-24, "Using a total of five spectrally distinguishable fluorochromes, 31 different

bar codes are created without using a given fluorochrome more than once in a given bar code. The creation of the 31 bar codes using 5 fluorochromes is an extension of the scheme illustrated in FIG. 1, where 15 qualitative bar codes are created using 4 fluorochromes. One of the 31 bar codes is assigned to each of the 31 target sequences.")

With regard to claims 2-3, Singer teaches single stranded nucleic acid probes (see column 8, lines 16-38, where the oligonucleotides were synthesized, which necessarily is single stranded).

With regard to claim 5, Singer teaches the use of a variety of fluorescent dyes such as Cy3, Cy5, etc (see column 3, lines 1-2, where these dyes are, of course, fluorescent dyes, but also will function as Raman tags).

With regard to claim 9, Singer teaches that the barcode binds via the oligonucleotide probe (see column 8, lines 39-43).

With regard to claim 10, Singer teaches that distinguishable barcodes can be generated using multiple copies of the same tag (see column 3, line 59 to column 4, line 6).

With regard to claims 11, 13, 14, 25, 26, Singer teaches a nucleic acid target and detection of the binding to the target (see column 8, lines 39-57).

With regard to claim 15, Singer teaches forming a polymer using monomeric units (see column 8, lines 16-37, where the oligonucleotide synthesizer forms a polymer of nucleotide monomers).

With regard to claims 16-17, Singer teaches monomeric units which comprise different raman tags (see column 3, lines 1-2, where these dyes are, of course, fluorescent dyes, but also will function as Raman tags and see column 8, lines 16-19).

With regard to claims 18, 20, Singer teaches attachment by an amino group, which is a spacer, after the standard commercial oligonucleotide synthesizer step of deprotection (see column 8, lines 32-34).

With regard to claims 19, 24, Singer teaches attachment after polymerization of the monomeric unit (see column 8, lines 32-38).

With regard to claim 21, Singer teaches formation of 31 different subsequences (see column 8, lines 16-32).

With regard to claims 22-23, Singer teaches formation of the oligonucleotide using automated DNA synthesizers, which inherently utilize bead based solid supports (see column 8, lines 32-35).

Singer does not teach the use of branched DNA probes.

Urdea teaches a method of claims 1 and 12 comprising:

(a) obtaining a barcode comprising two or more tags attached to an organic molecule backbone (see figure 11 and column 20, line 35 to column 21, line 49, where the AMP or comb probe is formed by the attachment of branches of

nucleotides, and where 14 different tags are attached to the nucleic acid backbone (see column 20, line 38, specifically)),

(b) binding the barcode to a target (see figure 11 and column 21, line 50 to column 22, line 7, where the probes are hybridized to a target),

(c) detecting the barcode bound to the target (see figure 11 and column 22, lines 8-20, where the barcodes are detected).

With regard to claims 2-3, Urdea teaches single stranded nucleic acid probes (see figure 11 and column 20, line 35 to column 21, line 37, where the oligonucleotides were synthesized, and shown as single stranded).

With regard to claim 5, Urdea teaches the use of nucleotide tags which are detected (see figure 11 and columns 20-22).

With regard to claims 6-7, Urdea teaches branched nucleic acids with branches located at predetermined sites along the backbone (see figure 11 and column 20, line 35 to column 21, line 40).

With regard to claim 9, Urdea teaches that the barcode binds via the oligonucleotide probe (see figure 11 and column 21, line 50 to column 22, line 7).

With regard to claim 10, Urdea teaches that distinguishable barcodes can be generated using multiple copies of the same tag (see figure 13, where binding of AMP 1 and AMP2 can be distinguished by LP1 and LP2).

With regard to claims 11, 13, 14, Urdea teaches a nucleic acid target and detection of the binding to the target (see figures 11 and 13 and column 21, line 50 to column 22, line 7).

With regard to claim 12, Urdea teaches a "container" and "probe section" where the tagged LP1 and LP2 probes are hybridized to the AMP probes to create a barcode (see figure 13).

Horn provides a specific motivation to apply the branched DNA (or bDNA) method of Urdea to in situ hybridization methods such as those of Singer (see paragraph 0110-0111).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Singer to use the sensitive branched DNA probes of Urdea as motivated by Urdea and Horn since Singer recognizes a need for sensitive detection, noting "An imaging technology preferred for sensitive, quantitative detection of fluorochromes is described in Femino (see column 6, lines 32-34). Urdea notes regarding Branched DNA probes that "The invention increases both the sensitivity and specificity of such assays, by reducing the incidence of signal generation that occurs in the absence of target, and does not involve a substantial increase in either time or cost relative to current assay configurations (see column 2, lines 46-51)." Consequently, Urdea informs the ordinary practitioner that branched DNA probes are desirable for a number of reasons including sensitivity and specificity and reduction in nonspecific signal and these are elements of interest to Singer, who is interested in sensitive quantitative detection in an in situ assay. Horn specifically motivates the use of branched DNA probes in in situ assays such as those

employed by Singer, noting "These results demonstrate the usefulness of bDNA in mapping small regions of DNA on a large backbone. Not only was the time to completion greatly shortened using bDNA (1 day or less) but the fluorescence signal using bDNA was considerably higher (see paragraph 0111)." So an ordinary practitioner, interested in sensitive detection using the bar code method of Singer, would have been motivated to further amplify the signal of the bar codes with branched DNA since Urdea indicated that branched DNA improved sensitivity and Horn expressly indicates that branched DNA use in in situ hybridization assays shortened the time to completion while also providing considerably greater fluorescence signal.

Response to Arguments

5. Applicant's arguments filed July 23, 2007 have been fully considered but they are not persuasive.

Applicant argues that the prior art did not teach the use of different barcodes on different molecules. This is simply not correct. Both Dimitrov in the first rejection and Singer in the second rejection teach the use of multiple dyes forming barcodes which are necessarily located at different positions on the organic molecule backbone. This is clearly seen in figure 1 of Dimitrov where the barcodes are located at different positions on the molecular backbone.

Further, there is no doubt that both Dimitrov and Singer teach barcodes where the number of barcodes exceeds the number of different types of tags attached to the plurality of barcodes. As cited in the rejection, Dimitrov expressly states "In this invention, various ratios of different label monomers bound to nucleic acids can be

combined to generate a diverse population of unique labels that can include up to 10^{17} or more unique labels. For example, a nucleic acid labeled with two fluorescein labeled nucleotides and three rhodamine labeled nucleotides will emit light at a different wavelength compared to a nucleic acid labeled with three fluorescein nucleotides and two rhodamine nucleotides. In another example, a nucleic acid could be labeled with different ratios of three or more label monomer:nucleotides which greatly increases the variety of unique labels that can be generated (see paragraph 0065)." So Dimitrov expressly teaches the situation where ratios of different labels are combined to provide a much larger number of different tags. Dimitrov recognizes that up to 10^{17} or more unique labels can be formed by the use of ratios of a much small number of labels.

Singer also addresses this point, noting in column 8, lines 16-24, "Using a total of five spectrally distinguishable fluorochromes, 31 different bar codes are created without using a given fluorochrome more than once in a given bar code. The creation of the 31 bar codes using 5 fluorochromes is an extension of the scheme illustrated in FIG. 1, where 15 qualitative bar codes are created using 4 fluorochromes. One of the 31 bar codes is assigned to each of the 31 target sequences."

Thus, the element upon which Applicant is relying is expressly taught by the prior art and the rejections are maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jeffrey Fredman
Primary Examiner
Art Unit 1637
8/29/07